The Association Between Hypocalcemia and Outcome in COVID-19 Patients: a Retrospective Study

Bhagwan Singh Patidar
All India Institute of Medical Sciences

Tapasyapreeti Mukhopadhayay
All India Institute of Medical Sciences

Arulselvi Subramanian (arulselvi.jpnatc@gmail.com)
All India Institute of Medical Sciences https://orcid.org/0000-0001-7797-6683

Riicha Aggarwal
All India Institute of Medical Sciences

Kapil Dev Soni
All India Institute of Medical Sciences

Neeraj Nischal
All India Institute of Medical Sciences

Debasis Sahoo
All India Institute of Medical Sciences

Surbhi Surbhi
All India Institute of Medical Sciences

Ravindra Mohan Pandey
All India Institute of Medical Sciences

Naveet Wig
All India Institute of Medical Sciences

Rajesh Malhotra
All India Institute of Medical Sciences

Anjan Trikha
All India Institute of Medical Sciences

Research Article

Keywords: Calcium, Coronavirus, Laboratory parameters, Mortality, NLR, Pandemic

Posted Date: March 16th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-302159/v1

Abstract

Background: Calcium has been shown to have a vital role in the pathophysiology of SARS-CoV and MERS-CoV diseases but less is known about hypocalcemia in COVID-19 patients and its association with the disease severity and the final outcome. Therefore, this study was conducted with an aim to assess the clinical features in the COVID-19 patients having hypocalcemia and to observe its impact on COVID-19 disease severity and final outcome.

Method: In this retrospective study, consecutive COVID-19 patients of all age groups were enrolled. Demographical, clinical and laboratory details were collected and analysed. On the basis of albumin-corrected calcium level patients were classified into normocalcemic (n=51) and hypocalcemic (n=110). Death was the primary outcome.

Results: The mean age of hypocalcemic were significantly lower ($p<0.05$). A significantly higher number of normocalcemic patients had severe COVID-19 disease(92.73%, $p<0.01$), had comorbidities (82.73%, $p<0.05$) and required ventilator support(39.09%, $p<0.01$)compared to the hypocalcemic patients. The mortality rate was significantly higher (33.63%, $p<0.05$) in the hypocalcemic patients when compared with the normocalcemic patients (15.69%).

Haemoglobin ($p<0.01$), hematocrit ($p<0.01$) and red cell count ($p<0.01$) were significantly lower with higher levels of absolute neutrophil count (<0.05) and neutrophil to lymphocyte ratio ($p<0.01$) in the hypocalcemic patients.

Albumin-corrected calcium level had a significant positive correlation with haemoglobin level, haematocrit, red cell count, total protein, albumin and albumin to globulin ratio and a significant negative correlation with absolute neutrophil count and neutrophil to lymphocyte ratio.

Conclusion: The disease severity, ventilator requirement and mortality were considerably higher in hypocalcemic COVID-19 patients.

Introduction

During the ongoing COVID-19 pandemic caused by the novel enveloped RNA beta-coronavirus named Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2), the world is facing unexpected challenges due to the previously unrecognized viral illness. It’s been almost a year since the cluster of pneumonia of unknown aetiology was found in Wuhan, China [1]. The World Health Organization (WHO)and Ministry of Health and Family Welfare, Government of India has regularly issued diagnosis and treatment recommendations for COVID-19 disease[2, 3].The disease is still spreading rapidly around the world with a mortality rate varying from 0.7–10% [4]. Various studies have described the clinical characteristics and discussed the potential early and sensitive biomarkers (like C-reactive protein, procalcitonin, interleukin-6, ferritin, D-dimer, lymphopenia, neutrophil to lymphocyte ratio etc.) to estimate the disease severity and prognosis of COVID-19 disease [5–10]. A very few studies have shown the

presence of higher incidence of hypocalcemia in COVID-19 patients and a higher rate of hospitalization in those patients. Some have highlighted the association of hypocalcemia with disease severity and poor prognosis in COVID-19 disease [11, 12]. Calcium has been shown to play a vital role in the patho-physiology of SARS-CoV and MERS-CoV diseases also [13, 14].

Thus there could be a possibility that hypocalcemia in COVID-19 patients may also be associated with higher disease severity and poor outcome. However, the available information concerning about this is not enough at present. Therefore, the aim of the present study was to assess the clinical features in COVID-19 patients having hypocalcemia and to determine its impact on COVID-19 disease severity and final outcome.

Materials And Methods

This is a retrospective descriptive observational study. The study was conducted at JPNATC, AIIMS,Delhi which is now a dedicated COVID-19 care centre during the pandemic. The patients are admitted here after being diagnosed COVID-19 positive by real-time polymerase chain reaction (RT-PCR) according to the WHO guidelines. Total 161 patients of all age groups admitted during the 23 March to 30 April, 2020 were enrolled in the study. They were classified into mild, moderate and severe COVID-19 disease according to the WHO and the Ministry of Health and Family Welfare, Government of India, guidelines [2, 3]. Demographical, clinical and laboratory details on the day of admission were collected from hospital data base and analysed thoroughly. On the basis of albumin-corrected calcium level, patients were classified into normocalcemic, (n = 51, albumin-corrected calcium level: 8.6–10.3 mg/dl) and hypocalcemic (n = 110, albumin-corrected calcium level: below 8.6 mg/dl). Albumin- corrected serum calcium was calculated by the formula: Albumin-corrected calcium (mg/dl) = Measured total calcium (mg/dl) + 0.8 (4.0 – serum albumin (g/dl). Death was the primary outcome. The secondary outcomes were severity of disease and requirement for ventilator support. The study was conducted after obtaining the approval from the Ethics Committee of the Institute. Patients with incomplete information were excluded from the study.

Statistical Analysis:

All statistical analyses were performed by GraphPad Prism 5.0 Software. Data are presented as count (percentages) for categorical variables. Results for continuous variables are expressed as mean ± SD or median ± IQR (Inter Quartile Range) as indicated. Categorical variables between groups are compared using the $\chi 2$ test or Fisher exact test, and continuous variables are analysed using Student's t test or Mann-Whitney U test as appropriate. The Pearson’s or spearman’s test was usedto determine the correlation coefficient. A value of $p < 0.05$ was considered statistically significant.

Results

Demographical and clinical characteristics in the hypocalcemic patients

Out of 161, 68.32% (110) patients were hypocalcemic. The mean age of the patients was 49.20 ± 17.07 years. Out of them, 21.82% patients were elderly and 67.27% were males. The mortality rate was 33.63%. Among the non-survivors hypocalcemic patients, 75.67% were malesand 40.54% were elderly.Of allthe hypocalcemic patients, 92.73% were classified as severe COVID-19 disease and 39.09% required ventilator support during the hospital stay. At least one comorbiditywas present in 82.73% of hypocalcemic COVID-19 patients. Diabetes, hypertension and malignancy present in 26.36%, 29.09% and 14.54% patients respectively.

Laboratory features in the hypocalcemic patients

The mean haemoglobin level was 10.31 ± 2.58 gm% in hypocalcemic patients. Of all, haemoglobin level was less than12gm% in 73.64% of the patients and less than 7gm% in10% of the patients. The mean packed cell volume was 31.34 ± 7.76 % and the mean red cell count was 3.59 ± 0.97 million cells/µl. The median leucocyte count was 9.55(6.8–12.3) $x10^3$cells/cumm and median neutrophil to lymphocyte ratio (NLR) was 2.78(1.79–4.75). The mean total calcium was 7.67 ± 0.69 mg/dl. We observed hypoproteinemia in 73.64%patients with 96.36% patients had hypoalbuminemia. Aspartate transaminase was increased in 63.64% patients. Uremia was observed in 39.09% patients.

Comparison between the normocalcemic and hypocalcemic patients

The details are given in Tables 1 and 2. The mean age of the normocalcemic patients was significantly lower than the hypocalcemic patients (43.35 ± 17.98 v/s 49.20 ± 17.07 years respectively;$p < 0.05$). Significantly higher number of patients (92.73%) in the hypocalcemic group were affected from severe COVID-19 disease compared to 76.47% in the normocalcemia group ($p < 0.01$). In comparison with the normocalcemic patient, higher number of hypocalcemic COVID-19 patients had comorbidities (82.73% v/s 64.70%, $p < 0.05$) and required ventilator support during treatment (39.09% v/s 15.69%, $p < 0.01$). The mortality rate was significantly higher ($p < 0.05$) in the hypocalcemic patients (33.63%) as compared to the normocalcemic patients (15.69%). Among the non-survivors hypocalcemic patients, 75.67% were males and 40.54% were elderly patients.

Table 1
Comparisons of demographical and clinical details of normocalcemic and hypocalcemic patients

Parameter	Normocalcemicpatients (n = 51)	Hypocalcemicpatients (n = 110)	p value
Age(years)	43.35 ± 17.98	49.20 ± 17.07	**< 0.05**
Elderly (> 60 years of age)	9 (17.65%)	24 (21.82%)	0.5419
Males	35(68.63%)	74 (67.27%)	0.8642
Comorbidities	33(64.70%)	91 (82.73%)	**< 0.05**
• **Diabetes Mellitus**	9(17.65%)	29 (26.36%)	0.2256
• **Hypertension**	12(23.53%)	32 (29.09%)	0.4613
• **Malignancy**	5(9.80%)	16 (14.54%)	0.4624
Severe patients	39(76.47%)	102 (92.73%)	**< 0.01**
Ventilator support	8(15.69%)	43 (39.09%)	**< 0.01**
Non-survivors	8(15.69%)	37 (33.63%)	**< 0.05**

Note: Continuous data are presented as mean ± standard deviation or median ± IQR (Inter Quartile Range). Categorical data are presented as frequency (%).

Table 2
Comparisons of laboratory parameters among normocalcemic and hypocalcemic patients

Parameter	Normocalcemic patients (n = 51)	Hypocalcemic patients(n = 110)	P Value
Hematological Parameters			
Haemoglobin (gm%)	11.64 ± 2.64	10.31 ± 2.58	**< 0.01**
Anemia (haemoglobin < 12 gm %)	23 (45.09%)	81 (73.64%)	**< 0.001**
Hematocrit %	35.32 ± 7.58	31.34 ± 7.76	**< 0.01**
Hematocrit < 38%	27 (52.94%)	88 (80%)	**< 0.001**
Red Blood Cells (million/µl)	4.10 ± 0.93	3.59 ± 0.97	**< 0.01**
Red Blood Cells < 4.5 million/µl)	27 (52.94%)	88 (80%)	**< 0.001**
Total Leucocyte Count (cells/µl)	7500 (5100–12100)	9550 (6800–12300)	0.1297
Leucocytosis > 11000 cells/µl	14 (27.45%)	34 (30.91%)	0.9040
Leucopenia < 4000 cells/µl	5 (9.8%)	10 (9.09%)	
Absolute neutrophil count	4500 (2838–7854)	5590 (3881–9143)	**< 0.05**
Absolute lymphocyte count	2268 (1504–3360)	2112 (1310–2913)	0.1668
Absolute monocyte count	384 (279–840)	545 (310–912)	0.1107
Absolute eosinophil count	166 (72–264)	122 (77–218)	0.4640
Neutrophil to lymphocyte ratio	2.13 (1.33–2.75)	2.78 (1.79–4.75)	**< 0.01**
Platelets($X10^3$cells/µl)	169.0 (122.0– 246.0)	168.0 (105.8-217.3)	0.2434
Thrombocytopenia < 150$X10^3$cells/µl)	19 (37.25%)	47 (42.73%)	0.6060
Coagulation Profile			
Prothrombin Time (Sec)	15.40 (12.70–20.60)	15.20 (12.80–17.60)	0.7743
Prolonged Prothrombine time	6 (11.76%)	8 (7.27%)	0.3467
Activated Partial Thromboplastin Time (sec)	32.65 (27.78–40.10)	30.10 (23.60–38.60)	0.2180
Prolonged aPTT	4 (7.84%)	10 (9.09%)	1.000
International Normalised Ratio	1.15 (0.93–1.57)	1.12 (0.93–1.31)	0.3425

Parameter	Normocalcemic patients (n = 51)	Hypocalcemic patients(n = 110)	P Value
Liver Function Test			
Bilirubin Total (mg/dl)	0.80 (0.60–0.90)	0.75 (0.50–1.20)	0.9948
Hyperbilirubinemia	10 (19.61%)	37 (33.64%)	0.0685
Total Protein (gm/dl)	6.62 ± 1.15	5.99 ± 0.95	**< 0.001**
Hypoproteinemia	21 (41.18%)	81 (73.64%)	**< 0.0001**
Albumin (gm/dl)	3.17 ± 0.85	2.51 ± 0.55	**< 0.0001**
Hypoalbuminemia	40 (78.43%)	106 (96.36%)	**< 0.0001**
Globulin (gm/dl)	3.44 ± 0.79	3.48 ± 0.76	0.7792
A/G Ratio	0.96 ± 0.33	0.75 ± 0.23	**< 0.0001**
Aspartate Transaminase (IU/L)	36 (26–75)	48 (30.00-75.50)	0.1247
High Aspartate Transaminase	23 (45.10%)	70 (63.64%)	**< 0.05**
Alanine Transaminase (IU/L)	32 (21–57)	34.00 (19.75–57.75)	0.9841
High Alanine Transaminase	17 (33.33%)	44 (40%)	0.4172
Alkaline Phosphatase (IU/L)	73 (62–108)	81.50 (58.0-117.8)	0.3762
High Alkaline Phosphatase	8 (15.69%)	25 (22.73%)	0.3032
Renal Function Test			
Urea (mg/dl)	32.00 (22.00–47.00)	36.00 (26.00-90.50)	0.0819
Uremia	11 (21.57%)	43 (39.09%)	**< 0.05**
Creatinine (mg/dl)	0.80 (0.50-1.00)	0.80 (0.60–1.85)	0.1481
Hypercreatinemia	10 (19.61%)	32 (29.09%)	0.2024
Uric Acid (mg/dl)	4.00 (3.50–5.30)	4.90 (3.57–7.62)	0.0712
Hypouricemia	1 (1.96%)	4 (3.64%)	0.1870
Hyperuricemia	7 (13.73%)	28 (25.45%)	
Calcium (mg/dl)	9.09 ± 0.44	7.67 ± 0.69	**< 0.0001**

Parameter	Normocalcemic patients (n = 51)	Hypocalcemic patients(n = 110)	P Value
Phosphate (mg/dl)	3.70 (2.80–4.60)	3.50 (2.57–5.25)	0.9638
Hypophosphatemia	11 (21.57%)	24 (21.82%)	0.8155
Hyperphosphatemia	13 (25.49%)	33 (30%)	
Electrolytes			
Sodium (mEq/L)	137.10 ± 5.63	134.90 ± 13.16	0.2485
Hyponatremia	16 (31.37%)	45 (40.91%)	0.4172
Hypernatremia	2 (3.92%)	6 (5.45%)	
Potassium (mEq/L)	4.31 ± 0.82	4.36 ± 0.89	0.7133
Hypokalemia	6 (11.77%)	14 (12.73%)	0.8632
Hyperkalemia	0 (0)	0 (0)	

Note: Continuous data are presented as mean±standard deviation or median ± IQR (Inter Quartile Range). Categorical data are presented as frequency (%).

Significantly lower haemoglobin levelwas observed in the hypocalcemic patients as compared to the normocalcmic patients ($p < 0.01$). Also, a considerably lower hematocrit ($p < 0.01$) and red cell count ($p < 0.01$) were found in the hypocalcemic COVID-19 patients. Significantly higher (73.64%) numbers of patients were presented with anemia in hypocalcemic group ($p < 0.01$). Absolute neutrophilcount (ANC)(< 0.05) and NLR($p < 0.01$) weresignificantly higherinthe hypocalcemic patients. Significantly lower levels of total protein and albumin were observed in the COVID-19 patients having hypocalcemia ($p < 0.001$ and $p < 0.0001$ respectively). In comparison of normocalcemic patients, significantly higher number of hypocalcemic patients had hypoproteinemia (73.64% v/s 41.18%, $p < 0.0001$) and hypoalbuminemia (96.36% v/s 78.43%, $p < 0.0001$). Albumin to globulin ratio was significantlydecreased in the hypocalcemic patients as compared to the normocalcemic patients ($p < 0.0001$). Raised aspartate transaminase were observed in 63.64% of hypocalcemic patients compared to 45.10% of normocalcemic patients ($p < 0.05$). 39.09% of hypocalcemic patients had uremia compared to 21.57% of normocalcemic patients ($p < 0.05$).

Correlation of albumin-corrected calcium with different laboratory parameters

Albumin corrected calcium level had significant positive correlation with haemoglobin level ($r = 0.20$, $p < 0.05$), hematocrit ($r = 0.22$, $p < 0.01$), red cell count ($r = 0.25$, $p < 0.01$), total protein ($r = 0.36$, $p < 0.0001$), albumin ($r = 0.46$, $p < 0.0001$) and albumin to globulin ratio ($r = 0.32$, $p < 0.0001$). Significant negative correlation of the total calcium was observed with ANC ($r= -0.17$, $p < 0.05$) and NLR ($r= -0.27$, $p < 0.001$) (Fig. 1).

Discussion

This study represents the first description of the hypocalcemic patients with COVID-19 disease from an apex COVID-19 care centre in north India. The trends in the study show that the COVID-19 positive patients with hypocalcemia were severely affected by the disease and more patients required ventilator support during the hospital stay. Higher mortality was found in the hypocalcemic patients and of all the non-survivors, more than one-third were elderly and more than three-forth were males. Similar to our finding, a study shows that hypocalcemia presents more frequently in maleCOVID-19 patients [12].

In the COVID-19 patients, hypocalcemia may be a result of an imbalance in parathyroid hormone and vitamin D levels in blood [15]. Also, the increased levels of unbound fatty acids and unsaturated fatty acids seen in severe COVID-19 patients may bind with the calcium and result into acute hypocalcemia [16]. In these patients, hypocalcemia positively correlates with reduced pulmonary functional index, lymphopenia, albumin levels, vitamin D levels and negatively correlates with parathyroid hormone, C-reactive protein, lactate dehydrogenase and D-dimer [11, 15, 17]. The current study also found a significant positive correlation between calcium and haemoglobin, hemtatocrit, red cell count, total protein level, albumin level and albumin to globulin ratio and significant a negative correlation of calcium with absolute neutrophil count and neutrophil to lymphocyte ratio.

The consequences inSARS-CoV-2 may be the same as SARS-CoV due to similarities in the genome of both the viruses [18].Various viral pneumonia present with hypocalcemia [19]. Hypocalcemia has been reported in 60% of SARS disease and 62% of Ebola virus disease[20]. Altered calcium concentrations are usually observed during host cell dysfunction after viral infections [21]. Viruses use the calcium signal to generate a better environment for their benefits [22]. Changes of ion homeostasis, mainly in calcium homeostasis promote the viral growth [23]. Forvariousenveloped viruses such as SARS-CoV, MERS-CoV and Ebolavirus, calcium plays a very important role in the viral fusion and promotes their replication by directly interacting with fusion peptides of these viruses [20]. By using the calcium signal system of the host, virus can affect the occurrence and progression of the disease [24]. Calcium is required for the virus structure formation, viral entry, gene expression, virion maturation and release. Calcium ion activity is demonstrated in small transmembrane protein coded by SARS-CoV E gene in animal models infected with SARS-CoV and its synthesis is increased during viral infection [18]. By using calcium channels or pump, viruses disturb the homeostasis of calcium in the body and induced host cell morbidity [21]. A high viral load and prolonged period of viral shedding may present in COVID-19 hypocalcemic patients. Along with hypochloremia and bilateral pneumonia, hypocalcemia on admission has been shown to be an independent risk factor for long-term hospitalization in COVID-19 patients[25].

Abnormal calcium level is commonly observed in the critically ill patients. Studies show the association of hyper and hypocalcemia with higher organ injury and increased mortality in critical illnesses [15, 26, 27]. Up to 85% of the critically ill patients have presented with hypocalcemia and have higher mortality [28]. Very high prevalence of hypocalcemia, nearly up to 80%, has also been observed in the COVID-19 patients [20]. In our study, we found two-thirds of the COVID-19 patients to behypocalcemic.

Hypocalcemia has been included among the two most powerful risk factors to assess the severity of COVID-19 disease along with dyspnoea [24].

Calcium levels should be monitored in all cases of acute and recovered COVID-19 patients [29]. Hospitalized patients with serum ionised calcium level below 4.80 mg/dl have increased risk of acute respiratory failure and had more requirement of mechanical ventilation [30]. Timely supplementation of calcium has been suggested in severe COVID-19 patients to prevent organ failure as an early diagnosis and treatment of hypocalcemia may alleviate organ injury [31].

Limitation and future needs: There were a few limitations in this study. One of the potential limitations of our study is that our data comes from a single center study, and the sample size is relatively small, we believe that larger studies are needed to confirm our findings. In addition, measurement of ionized serum calcium should be done because it is more accurate than albumin-corrected calcium. And further studies are needed to find the causes of hypocalcemiain COVID-19 patients and to see whether the correction of hypocalcemia would lead to the improvement of outcomes.

Conclusion

Theseverity, ventilator requirement and mortality were considerably higher in the hypocalcemic COVID-19 patients. The current study indicates age, comorbidities, low haemoglobin level, higher neutrophil to lymphocyte ratio, and hypoalbuminemia are associated with the poor outcome.

Declarations

- **Funding Sources:** None
- **Conflicts of Interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.
- **Availability of data and material:** available if required. Confidentiial
- **Code availability:** nil
- **Authors contributions:** BSP wrote the manuscript; BSP, TM, AS did data analysis; BSP, TM, RA, KS, NN, DS, Surbhi helped in data collection, clinical correlation and interpretation; RMP helped in statistical studies and interpretation; NW,RM, AT helped in editing/review of the manuscript. AS is guarantee for the study.
- **Ethics Approval:** The study was conducted after obtaining the approval from the ‘Institutional Ethics Committee’.
- **Consent to participate:** Informed and written consent is not needed from study subject.
- **Consent for publication:** Not applicable

References

1. Hussain A, Bhowmik B, do Vale Moreira NC. COVID-19 and diabetes: Knowledge in progress. Diabetes Res Clin Pract. 162, 108142 (2020).
2. World Health Organization. https://www.who.int/. Accessed 03 November 2020.
3. Ministry of Health & Family Welfare, Government of India. https://www.mohfw.gov.in/. Accessed 03 November 2020.
4. Pal R, Bhadada SK. COVID-19 and diabetes mellitus: An unholy interaction of two pandemics. Diabetes Metab Syndr. 14(4), 513-17 (2020).
5. Fang Z, Yi F, Wu K, Lai K, Sun X, Zhong N, Liu Z. Clinical characteristics of 2019 coronavirus pneumonia (COVID-19): an updated systematic review. MedRxiv. 2020. https://doi.org/10.1101/2020.03.07.20032573.
6. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DS, Du B. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 382(18), 1708-20 (2020).
7. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, Satlin MJ, Campion Jr TR, Nahid M, Ringel JB, Hoffman KL. Clinical characteristics of Covid-19 in New York city. N Engl J Med. 382, 2372-74 (2020).
8. Zou L, Dai L, Zhang Y, Fu W, Gao Y, Zhang Z, Zhang Z. Clinical Characteristics and Risk Factors for Disease Severity and Death in Patients With Coronavirus Disease 2019 in Wuhan, China. Front Med. 7, 532 (2020).
9. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, Li Q, Jiang C, Zhou Y, Liu S, Ye C. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 81(2), e16-e25 (2020).
10. Huang I, Pranata R, Lim MA, Oehadian A, Alisjahbana B. C-reactive protein, procalcitonin, D-dimer, and ferritin in severe coronavirus disease-2019: a meta-analysis. Ther Adv Respir Dis. 14, 1-14 (2020).
11. Mikhail N, Wali S. Clinical Significance of Hypocalcemia in COVID-19. Clin Res Diabetes Endocrinol. 3(1), 1-3 (2020).
12. Di Filippo L, Formenti AM, Rovere-Querini P, Carlucci M, Conte C, Ciceri F, Zangrillo A, Giustina A. Hypocalcemia is highly prevalent and predicts hospitalization in patients with COVID-19. Endocrine. 68, 475-78 (2020).
13. Millet JK, Whittaker GR. Physiological and molecular triggers for SARS-CoV membrane fusion and entry into host cells. Virology. 517, 3-8 (2018).
14. Straus MR, Tang T, Lai AL, Flegel A, Bidon M, Freed JH, Daniel S, Whittaker GR. Ca2+ ions promote fusion of Middle East Respiratory Syndrome coronavirus with host cells and increase infectivity. J Virol. 94(13), e00426-20 (2020).
15. Sun JK, Zhang WH, Zou L, Liu Y, Li JJ, Kan XH, Dai L, Shi QK, Yuan ST, Yu WK, Xu HY. Serum calcium as a biomarker of clinical severity and prognosis in patients with coronavirus disease 2019. Aging (Albany NY). 12(12), 11287 (2020).

16. Singh VP, Khatua B, El-Kurdi B, Rood C. Mechanistic basis and therapeutic relevance of hypocalcemia during severe COVID-19 infection. Endocrine. 70, 461–462 (2020).
17. Yang C, Ma X, Wu J, Han J, Zheng Z, Duan H, Liu Q, Wu C, Dong Y, Dong L. Low serum calcium and phosphorus and their clinical performance in detecting COVID-19 patients..J Med Virol. 2020; https://doi.org/10.1002/jmv.26515
18. Cappellini F, Brivio R, Casati M, Cavallero A, Contro E, Brambilla P. Low levels of total and ionized calcium in blood of COVID-19 patients. Clin Chem Lab Med. 58(9), e171–e173 (2020).
19. Sankaran RT, Mattana J, Pollack S, et al. Laboratory abnormalities in patients with bacterial pneumonia. Chest. 111, 595–600 (1997).
20. Marazuela M, Giustina A, Puig-Domingo M. Endocrine and metabolic aspects of the COVID-19 pandemic. Rev Endocr Metab Disord. 21(4), 495-507 (2020).
21. Chen X, Cao R, Zhong W. Host Calcium Channels and Pumps in Viral Infections. Cells. 9(1), 94 (2020).
22. Zhou Y, Frey TK, Yang JJ. Viral calciomics: interplays between Ca2+ and virus. Cell Calcium. 46(1), 1-7 (2009).
23. Nieto-Torres JL, Verdiá-Báguena C, Jimenez-Guardeño JM, Regla-Nava JA, Castaño-Rodriguez C, Fernandez-Delgado R, Torres J, Aguilella VM, Enjuanes L. Severe acute respiratory syndrome coronavirus E protein transports calcium ions and activates the NLRP3 inflammasome. Virology. 485, 330-9 (2015).
24. Hu C, Su F, Dai J, Lu S, Wu L, Chen D, Song Q, Zhou F. Prediction Model of Severe Coronavirus Disease 2019 (COVID-19) Cases Shows the Leading Risk Factor of Hypocalcemia. Research Square. 2020. https://doi.org/10.21203/rs.3.rs-41318/v1.
25. Wu Y, Hou B, Liu J, Chen Y, Zhong P. Risk factors associated with long-term hospitalization in patients with COVID-19: a single-centered, retrospective study. Front Med. 7, 315 (2020).
26. Wang B, Li D, Gong Y, Ying B, Cheng B. Association of serum total and ionized calcium with all-cause mortality in critically ill patients with acute kidney injury. Clin Chim Acta. 494, 94-9 (2019).
27. Wang B, Gong Y, Ying B, Cheng B. Association of initial serum total calcium concentration with mortality in critical illness. BioMed Res Int. 2018; https://doi.org/10.1155/2018/7648506.
28. Bullard Z, Dattero J, Zimmerman LH, Steelman J, Jurado L. 290: IN-HOSPITAL HYPOCALCEMIA: IS INTRAVENOUS CALCIUM HARMFUL? Crit Care Med. 47(1), 126 (2019).
29. Velayoudom FL, PS AW, Ranathunga HI, Somasundaram N. Endocrine vigilance in COVID-19. JPMA. J Pak Med Assoc. 70(5), S83-6 (2020).
30. Thongprayoon C, Cheungpasitporn W, Chewcharat A, Mao MA, Kashani KB. Serum ionised calcium and the risk of acute respiratory failure in hospitalised patients: a single-centre cohort study in the USA. BMJ open. 10(3), e034325 (2020).
31. Singh VP, Khatua B, El-Kurdi B. Hypocalcemia and hypoalbuminemia during COVID-19 infection: Opportunities for therapeutic intervention. J Infect Public Health. 2020.

https://doi.org/10.1016/j.jiph.2020.09.019.

Figures

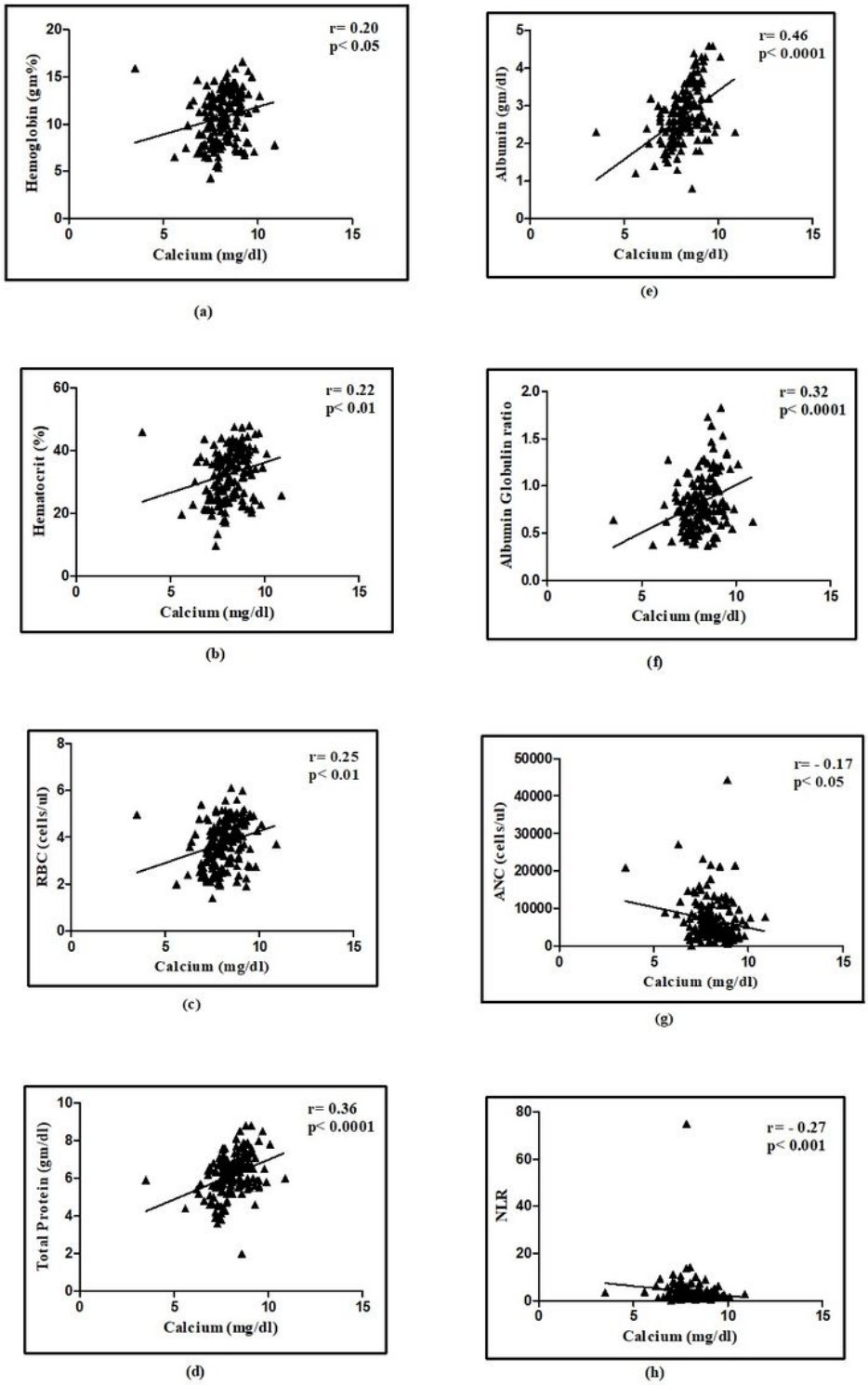

Figure 1

Correlation of albumin corrected calcium with different laboratory parameters